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| (54) Title: N ¹ -MODIFIED GLYCOPEPTIDES (57) Abstract The present invention is directed to N ¹ -acylated derivatives of desleucylA82846B. These derivatives are useful as antibacterials. | | |

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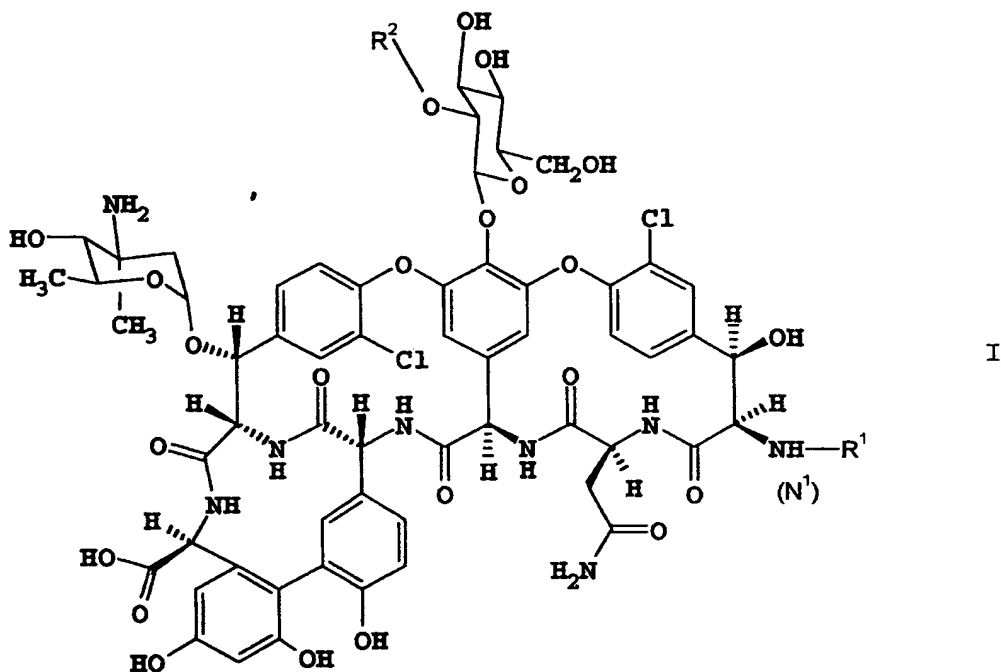
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N¹-MODIFIED GLYCOPEPTIDES

The present invention is directed to glycopeptides and is directed in particular to modifications of A82846B and its N^{DISACC} variations. In the claimed compounds, the original N¹ amino acid, N-methyl-D-leucine, has been removed and replaced with an acyl group or with an acyl group derived from an alternate α -amino acid.

10 The present invention is directed to compounds of the formula



wherein R¹ represents

alkanoyl of C₂-C₁₀ which is unsubstituted, or which is substituted by a phenyl, or which is substituted on other than the α -carbon atom by an amino or protected amino group;

15 benzoyl or substituted benzoyl bearing one or two substituents each of which is independently halo, loweralkyl of C₁-C₄, loweralkoxy of C₁-C₄ or phenyl;

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an acyl derived from an α -amino acid or an acyl derived from a protected α -amino acid, said α -amino acid being selected from the group consisting of:

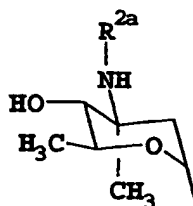
alanine,
5 arginine,
asparagine,
aspartic acid,
cysteine,
glutamic acid,
10 glutamine,
glycine,
histidine,
isoleucine,
leucine,
15 lysine,
methionine,
3-phenylalanine,
3-(p-chlorophenyl) alanine,
proline,
20 serine,
threonine,
tryptophan and
valine,

in either D- or L-form; or

25 an acyl derived from an α -amino acid as defined above which bears on the amine a substituent which is alkyl of C_1 - C_{10} , benzyl, phenylbenzyl, or p-chlorobenzyl, with the proviso that the acyl derived from N-methyl-D-leucine is excluded;

30 R^2 represents hydrogen, or epivancosaminy of the formula

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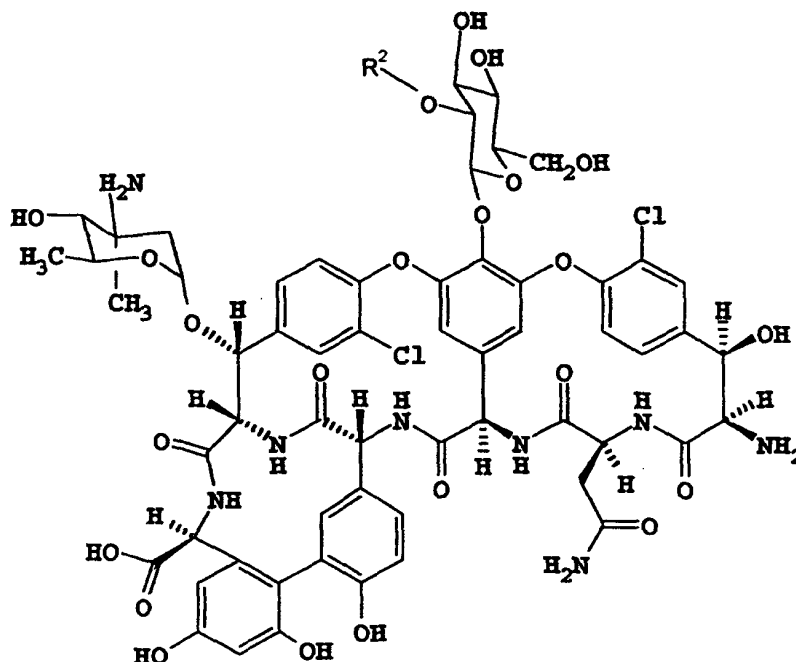


Wherein R^{2a} represents hydrogen or $-\text{CH}_2-\text{R}^3$; and R^3 represents
hydrogen,
5 alkyl of C_1-C_{11} ,
 alkyl of $\text{C}_1-\text{C}_{11}-\text{R}^4$, or
 $\text{R}^4 - (\text{linker})_{(0 \text{ or } 1)} - \text{R}^4$ or 1,
wherein each R^4 is independently phenyl or phenyl
substituted by one or two substituents, each of which is
10 independently halo, loweralkyl of C_1-C_8 , loweralkoxy of C_1-
 C_8 , loweralkylthio of C_1-C_4 , or trifluoromethyl, and
"linker" is $-\text{O}-$, $-\text{CH}_2-$, or $-\text{O}-(\text{CH}_2)_n-$ wherein n is 1-3;
and the pharmaceutically acceptable salts thereof.

When R^1 represents alkanoyl of C_2-C_{10} , it can be a
15 straight-chain alkanoyl, or it can be an alkanoyl which is
branched to any degree. Likewise, when R^3 represents alkyl
of C_1-C_{11} , it can be straight-chain or branched.

The compounds of the present invention are prepared
from the corresponding "A82846B hexapeptides" of the
20 formula:

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II

wherein R^2 is as defined above. These "A82846B

hexapeptides" are so called because the normal N^1 amino acid
 5 N-methyl-D-leucine, has been removed, reducing the number of
 amino acids in the parent glycopeptide from seven to six.

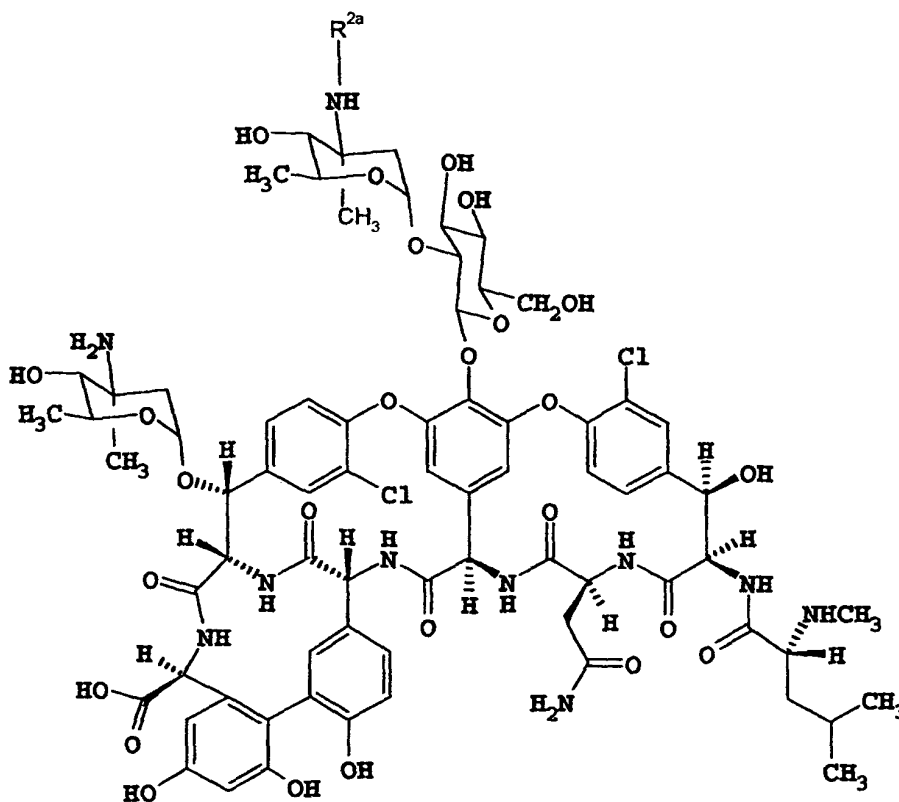
The compounds of the present invention are prepared by
 reacting an A82846B hexapeptide with an activated ester of
 an alkanolic acid of the desired acyl group R^1 . By

10 "activated ester" is meant an ester which renders the
 carboxyl function more reactive to coupling with the amine
 of the A82846B hexapeptide. The reaction of the A82846B
 hexapeptide and activated ester is carried out in an organic
 solvent, suitably a polar solvent such as dimethylformamide,
 15 dimethyl sulfoxide, or a mixture of dimethylformamide and
 dimethyl sulfoxide. The reaction proceeds under
 temperatures of a wide range, such as 25° to 100° C., but is

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preferably carried out at temperatures of about 25° to 35° C. Some of the desired product is produced shortly upon contacting the reactants, but higher yields are obtained with reaction times of from about 1 to about 24 hours, oftentimes from about 1 to about 5 hours. Isolation and purification are carried out under conventional procedures.

The starting A82846B hexapeptides are themselves synthesized from the parent glycopeptides:

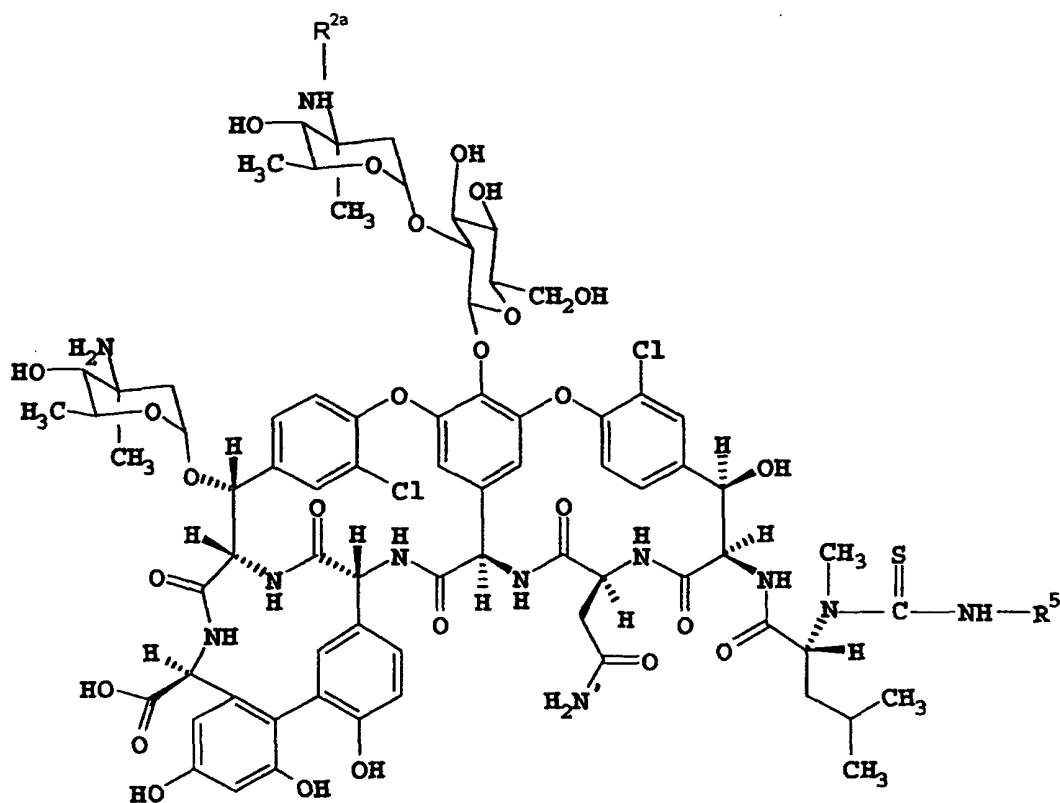


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wherein R^{2a} is as defined above. This synthesis is by the "Edman degradation", a two-step process for the cleavage of the N-terminal residue of a peptide or protein. The above parent glycopeptide is first reacted with an isothiocyanate of the formula $SCN-R^5$, to obtain an intermediate N^{LEU} - (thiocarbamoyl)-A82846B compound of the formula

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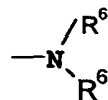
In the foregoing formula, R^5 represents

alkyl of C_1 - C_{10} ,

5 phenyl,

naphthyl, or

phenyl substituted by one or two substituents, each of which is independently halo, loweralkyl of C_1 - C_4 , loweralkoxy of C_1 - C_4 , benzyloxy, nitro, or



10

wherein each R^6 is independently loweralkyl of C_1 - C_4 .

This reaction is conveniently carried out in water with pyridine, at a temperature of 25° - 30° C, employing a slight excess of the isothiocyanate reactant. The N^{LEU} -

15 (thiocarbamoyl)A82846B intermediate can be separated in conventional manner or can be employed after removal of

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reaction solvent in the second step of the Edman degradation.

In the second step, the N^{LEU}-(thiocarbamoyl)A82846B is reacted with an organic acid, preferably trifluoroacetic acid, in a non-polar solvent such as dichloromethane. The reaction proceeds at temperatures of from 0°C to 35°C but is preferably carried out at temperatures of from 0°C to 25°C. The reaction is generally complete in several hours. The resulting hexapeptide product is separated and purified if desired in conventional procedures.

The second step of the Edman degradation can in some instances result in loss of the disaccharide epivancosamine. Longer reaction times can be used to obtain the des-epivancosaminyl compound (R^2 =hydrogen).

Other variations at the disaccharide position of the molecule can be obtained in conventional procedures. As described above, the Edman degradation and subsequent acylation can be carried out with the naturally-occurring disaccharide (R^2 =epivancosaminyl with R^{2a} =H) or with a disaccharide derivative (R^2 =epivancosaminyl with R^{2a} =CH₂-R³). This approach to synthesis of the present compounds is illustrated by the preparations below of Examples 12 and 26. However, it is also possible to prepare those claimed compounds with a disaccharide derivative (R^2 =epivancosaminyl with R^{2a} =-CH₂-R³) by first conducting the Edman degradation

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and subsequent acylation on A82846B, with its naturally occurring R^2 =epivancosaminy1, and thereafter introducing the desired epivancosaminy1 substituent $-CH_2-R^3$. This is illustrated by Examples 34 and 35.

- 5 Whether the $-CH_2-R^3$ substituent is introduced prior to Edman degradation and acylation, or after, the same conventional process is used. In this process, the substrate compound is reductively alkylated with the aldehyde suitable to introduce the desired $-CH_2-R^3$ group.
- 10 This process is taught in various references, see U.S. 5,591,714, and EPO 667,353.

The compounds of the present invention readily form salts, which can be prepared in conventional manner.

- 15 The following examples illustrate the preparation of the compounds of the present invention.

Preparation of N^{LEU} -(phenylthiocarbamoyl)- N^{DISACC} -

(p-(p-chlorophenyl)benzyl)A82846B

N^{DISACC} -(p-(p-Chlorophenyl)benzyl)A82846B

- 20 trihydrochloride (100.0 mg, 0.0526 mmol) was dissolved in 10 ml H_2O - pyridine (1:1 v/v) and treated with phenyl isothiocyanate (0.010 ml, 0.083 mmol). The resulting mixture was stirred at room temperature for 1 hr at which time HPLC analysis indicated complete consumption of the
- 25 starting material. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC to give 76.6 mg (76% yield) of the title compound. FAB-MS: calc. for $C_{93}H_{102}Cl_3N_{11}O_{26}S$ 1925.5, obtained 1928.5 (M+3).

Preparation of N^{DISACC}-(p-(p-chlorophenyl)benzyl)-
desleucylA82846B

5 from isolated thiourea

A sample of the purified N^{LEU}-(phenylthiocarbamoyl)-
N^{DISACC}-(p-(p-chlorophenyl)benzyl)A82846B (63.3 mg, 0.0327
mmol) was suspended in 10 ml CH₂Cl₂, cooled to 0 °C, then
treated with trifluoroacetic acid (0.10 ml). After 1 hr the
10 reaction mixture was warmed to room temperature and stirred
an additional 2 hr. The solvent was removed *in vacuo* and
the crude product was purified by preparative HPLC to give
25.3 mg (46% yield) of the title compound as a white powder.
FAB-MS: calc. for C₇₉H₈₄Cl₃N₉O₂₅ 1663.5, obtained 1666.4
15 (M+3).

Preparation of N^{DISACC}-(p-phenylbenzyl)desleucylA82846B
without isolation of thiourea intermediate

N^{DISACC}-(p-Phenylbenzyl)A82846B (41.0 mg, 0.0233 mmol)
20 was dissolved in 4 ml H₂O - pyridine (1:1 v/v) and treated
with phenyl isothiocyanate (0.0040 ml, 0.033 mmol). The
resulting mixture was stirred at room temperature for 3 hr
at which time HPLC analysis indicated complete consumption
of the starting material. The reaction mixture was
25 concentrated *in vacuo* to give the crude thiourea
intermediate as a white solid. The thiourea derivative was
then suspended in 10 ml CH₂Cl₂, cooled to 0 °C, then treated
with trifluoroacetic acid (0.25 ml). After 30 minutes the
reaction mixture was warmed to room temperature and stirred
30 an additional 1 hr. The solvent was removed *in vacuo* and

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the crude product was purified by preparative HPLC to give 14.0 mg (37% yield) of the title compound as a white powder. FAB-MS: calc. for $C_{79}H_{85}Cl_2N_9O_{25}$ 1629.5, obtained 1632.5 (M+3).

5

Preparation of Example 1

A sample of desleucylA82846B (101 mg, 0.0689 mmol) and the hydroxybenzotriazole hydrate active ester of 4-phenylbenzoic acid (47 mg, 0.149 mmol) was dissolved in 10 ml DMF. The resulting mixture was stirred at room temperature for 2 hours at which time HPLC analysis revealed complete consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product was purified by preparative HPLC to give 14 mg (12% yield) of N¹-(p-phenylbenzoyl)desleucylA82846B.

15

Preparation of Example 26

A sample of N^{DISACC}-(p-phenylbenzyl)desleucylA82846B (140 mg, 0.0858 mmol) and the hydroxybenzotriazole hydrate active ester of N-BOC-D-proline (66 mg, 0.199 mmol) was dissolved in 12 ml DMF. The resulting mixture was stirred at room temperature for 1 hour at which time HPLC analysis revealed consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product purified by preparative HPLC to give 77.5 mg (49% yield) of N¹-(N-BOC-D-proline) derivative of N^{DISACC}-(p-phenylbenzyl)desleucylA82846B.

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Preparation of Example 12

A sample of purified N¹-(N-BOC-D-proline) derivative of N^{DISACC}-(p-phenylbenzyl)desleucylA82846B (52.5 mg, 0.0287

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mmol) was suspended in 9 ml CH_2Cl_2 , cooled to 0° C, then treated with trifluoroacetic acid (0.5 ml). After 10 minutes the reaction mixture was warmed to room temperature and stirred for an additional 50 minutes. HPLC analysis revealed complete consumption of the starting material. The solvent was removed *in vacuo*, and the crude product was purified by preparative HPLC to give 15 mg (30% yield) of N^1 -D-proline derivative of N^{DISACC} -(p-phenylbenzyl)desleucylA82846B.

10

Preparation of Examples 34 and 35

A sample of N^1 -D-leucine derivative of desleucylA82846B (95 mg, 0.0602 mmol) and p-phenylbenzaldehyde (14 mg, 0.0768 mmol) was dissolved in 10 ml N,N-dimethylformamide (DMF) and 10 ml methanol (MeOH). The resulting mixture was heated to 75°C and stirred for 1 hour 15 minutes. At this time, sodium cyanoborohydride (26 mg, 0.413 mmol) was added and the reaction stirred at 75°C for another 1 hour 30 minutes at which time HPLC analysis revealed consumption of the starting material. The reaction mixture was concentrated *in vacuo* and the crude product purified by preparative HPLC to give 32 mg (30%) of N^1 -(N-p-phenylbenzyl)-D-leucine derivative of desleucylA82846B and 3 mg (2.6%) of N^{DISACC} -(p-phenylbenzyl)- N^1 -(N-p-phenylbenzyl)-D-leucine derivative of desleucylA82846B.

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The HPLC procedures reported in these examples were as follows:

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Analytical: Reactions were monitored by analytical HPLC using a Waters C₁₈ μ Bondapak or Novapak C₁₈ column (3.9x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH₃CN - 95% buffer to 80% CH₃CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H₃PO₄.

Preparative: Crude reaction mixtures were purified by preparative HPLC using a Waters C₁₈ Nova-Pak column (40x300 mm) and UV detection at 280 nm. Elution was accomplished with a linear gradient of 5% CH₃CN - 95% buffer to 80% CH₃CN - 20% buffer over 30 minutes. The buffer used was 0.5% triethylamine in water, adjusted to pH 3 with H₃PO₄. The desired fractions were subsequently desalted with a Waters C₁₈ Sep-Pak (35 cc) followed by lyophilization.

Compounds were desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH₃CN/H₂O, CH₃CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

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Representative compounds of the present invention are listed in the following tables:

TABLE I: SIMPLE ACYL DERIVATIVES

| Example # | FAB-MS | M + X | HPLC, min | Compound Name |
|-----------|--------|-------|-----------|--|
| 1 | 1644.2 | 1 | 14.7 | N ¹ -(p-phenylbenzoyl)desleucylA82846B |
| 2 | 1667.4 | 2 | 17.3 | N ¹ -(8-phenyl-n-octanoyl)desleucylA82846B |
| 3 | 1834.7 | 3 | 20.4 | N ¹ -(8-phenyl-n-octanoyl)-N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 4 | 1564.4 | 3 | 11.0 | N ¹ -(4-methyl-n-pentanoyl)desleucylA82846B |
| 5 | 1730.4 | 3 | 17.3 | N ¹ -(4-methyl-n-pentanoyl)-N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 6 | 1812.7 | 3 | 18.9 | N ¹ -(p-phenylbenzoyl)-N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 7 | 1764.4 | 0 | 18.7 | N ¹ -(4-methyl-n-pentanoyl)-N ^{DISACC} -[p-(p-chlorophenyl)benzyl]desleucylA82846B |
| 8 | 1868.5 | 3 | 23.0 | N ¹ -(8-phenyl-n-octanoyl)-N ^{DISACC} -[p-(p-chlorophenyl)benzyl]desleucylA82846B |
| 9 | 1892.9 | 2 | 21.1 | N ¹ -[7-(tert-butoxycarboxamido)-n-heptanoyl]-N ^{DISACC} -[p-(p-chlorophenyl)benzyl]desleucylA82846B |
| 10 | 1793.5 | 3 | 14.9 | N ¹ -(7-amino-n-heptanoyl)-N ^{DISACC} -[p-(p-chlorophenyl)benzyl]desleucylA82846B |

TABLE II: AMINO ACID DERIVATIVES

| Example # | FAB-MS | M + X | HPLC, min | Compound Name |
|-----------|--------|-------|-----------|---|
| 11 | 1845.5 | 3 | 18.3 | N ¹ -(N-BOC-L-leucine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 12 | 1729.3 | 3 | 14.2 | N ¹ -D-proline derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 13 | 1745.4 | 3 | 14.2 | N ¹ -D-leucine derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 14 | 1679.6 | 3 | 13.3 | N ¹ -(N-BOC-D-leucine) derivative of desleucylA82846B |
| 15 | 1863.3 | 3 | 18.0 | N ¹ -(N-BOC-D-methionine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 16 | 1794.7 | 3 | 14.9 | N ¹ -(N,N'-DIBOC-D-lysine) derivative of desleucylA82846B |
| 17 | 1579.2 | 3 | 8.5 | N ¹ -D-leucine derivative of desleucylA82846B |
| 18 | 1845.5 | 3 | 18.3 | N ¹ -(N-BOC-D-leucine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 19 | 1960.4 | 3 | 19.2 | N ¹ -(N,N'-DIBOC-D-lysine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 20 | 1747.2 | 3 | 15.6 | N ¹ -(N-BOC-D-3-(p-chlorophenyl)alanine) derivative of desleucylA82846B |
| 21 | 1913.5 | 3 | 19.6 | N ¹ -(N-BOC-D-3-(p-chlorophenyl)alanine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 22 | 1813.5 | 3 | 14.4 | N ¹ -(D-3-(p-chlorophenyl)alanine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |

TABLE II (continued)

| Example # | FAB-MS | M + X | HPLC, min | Compound Name |
|-----------|--------|-------|-----------|---|
| 23 | 1760.4 | 3 | 12.9 | N ¹ -D-lysine derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 24 | 1663.1 | 3 | 11.6 | N ¹ -(N-BOC-D-proline) derivative of desleucylA82846B |
| 25 | 1919.3 | 4 | 18.7 | N ¹ -(N-BOC-D-tryptophan) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 26 | 1830.1 | 3 | 17.7 | N ¹ -(N-BOC-D-proline) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 27 | 1745.2 | 3 | 15.1 | N ¹ -L-leucine derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 28 | 1913.4 | 3 | 19.4 | N ¹ -(N-BOC-L-3-(p-chlorophenyl)alanine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 29 | 1829.5 | 3 | 17.1 | N ¹ -(N-BOC-L-proline) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 30 | 1960.5 | 3 | 19.1 | N ¹ -(N'-DIBOC-L-lysine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 31 | 1760.4 | 3 | 13.3 | N ¹ -L-lysine derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 32 | 1729.4 | 3 | 14.3 | N ¹ -L-proline derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 33 | 1813.3 | 3 | 16.2 | N ¹ -(L-3-(p-chlorophenyl)alanine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |

TABLE II (Continued)

| Example # | FAB-MS | M + X | HPLC, min | Compound Name |
|-----------|--------|-------|-----------|--|
| 34 | 1745.4 | 3 | 13.3 | N ¹ -(N-(p-phenylbenzyl)-D-leucine) derivative of desleucylA82846B |
| 35 | 1911.6 | 3 | 17.9 | N ¹ -(N-(p-phenylbenzyl)-D-leucine) derivative of N ^{DISACC} -(p-phenylbenzyl)desleucylA82846B |
| 36 | 1536.5 | 3 | 16.5 | N ¹ -(N-BOC-D-leucine) derivative of desepivancosaminyl desleucylA82846B |
| 37 | 1436.3 | 3 | 9.1 | N ¹ -D-leucine derivative of desepivancosaminyl-desleucylA82846B |
| 38 | 1747.4 | 3 | 14.5 | N ¹ -(N-n-hexyl-D-leucine) derivative of N ^{DISACC} -n-hexyl desleucylA82846B |
| 39 | 1661.7 | 1 | 11.0 | N ¹ -(N-n-hexyl-D-leucine) derivative of desleucylA82846B |
| 40 | 1727.3 | 3 | 14.8 | N ¹ -(N-BOC-N-methyl-D-phenylalanine) derivative of desleucylA82846B |
| 41 | 1679.2 | 3 | 14.1 | N ¹ -(N-BOC-N-methyl-D-valine) derivative of desleucylA82846B |
| 42 | 1577.3 | 1 | 7.7 | N ¹ -(N-methyl-D-valine) derivative of desleucylA82846B |

The compounds of the present invention are useful for the treatment of bacterial infections. Therefore, in another embodiment, the present invention is directed to a method for controlling a bacterial infection in a host
5 animal, typically a warm-blooded animal, which comprises administering to the host animal an effective, antibacterial amount of a compound of the present invention. In this embodiment, the compounds can be used to control and treat infections due to various bacteria, but especially gram-
10 positive bacteria. In a preferred embodiment, the compounds are used to control and treat infections due to bacteria resistant to existing antibacterials. For example, certain bacteria are resistant to methicillin, and yet others are resistant to vancomycin and/or teicoplanin. The present
15 compounds provide a technique for controlling and treating infections due to such resistant bacterial species.

In carrying out this embodiment of the invention, the compounds of the present invention can be administered by any of the conventional techniques, including the oral route
20 and parenteral routes such as intravenous and intramuscular. The amount of compound to be employed is not critical and will vary depending on the particular compound employed, the route of administration, the severity of the infection, the interval between dosings, and other factors known to those
25 skilled in the art. In general, a dose of from about 0.5 to about 100 mg/kg will be effective; and in many situations, lesser doses of from about 0.5 to about 50 mg/kg will be effective. A compound of the present invention can be administered in a single dose, but in the known manner of

antibacterial therapy, a compound of the present invention is typically administered repeatedly over a period of time, such as a matter of days or weeks, to ensure control of the bacterial infection.

5 Also in accordance with known antibacterial therapy, a compound of the present invention is typically formulated for convenient delivery of the requisite dose. Therefore, in another embodiment, the present invention is directed to a pharmaceutical formulation comprising a compound of the
10 present invention, in combination with a pharmaceutically-acceptable carrier. Such carriers are well known for both oral and parenteral routes of delivery. In general, a formulation will comprise a compound of the present invention in a concentration of from about 0.1 to about 90%
15 by weight, and often from about 1.0 to about 3%.

The antibacterial efficacy of the present compounds is illustrated by Table III. The minimal inhibitory concentrations (MICs) were determined using a standard broth micro-dilution assay.

TABLE III: ACTIVITY OF SIMPLE ACYL DERIVATIVES*

| Example # | Resistant | Sensitive | SA 446 | SA 489 | SA 447 | SA X400 | SA X778 | SA 491 | SA S13E | SA 1199 |
|-----------|-----------|-----------|--------|--------|--------|---------|---------|--------|---------|---------|
| 1 | >128 | 4 | 1 | 0.5 | 0.25 | 0.5 | 0.125 | 0.5 | 0.25 | 0.125 |
| 2 | >128 | 1.5 | ≤.06 | ≤.06 | ≤.06 | ≤.06 | ≤.06 | ≤.06 | ≤.06 | 0.125 |
| 3 | 6.7 | 2.6 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 |
| 4 | >128 | 4 | 1 | 0.5 | 1 | 0.25 | 0.5 | 0.125 | 0.5 | 0.5 |
| 5 | 27 | 0.44 | 0.125 | 0.125 | ≤.06 | ≤.06 | 0.125 | ≤.06 | 0.125 | 0.25 |
| 6 | 38 | 3.5 | 1 | 2 | 2 | 1 | 0.5 | 0.5 | 1 | 0.5 |
| 7 | 3.4 | 0.22 | 0.5 | 1 | 0.5 | 0.5 | 1 | 0.125 | 0.5 | 1 |
| 8 | 4 | 2 | 16 | 8 | 8 | 8 | 4 | 4 | 8 | 4 |
| 9 | 4.8 | 0.66 | 2 | 1 | 2 | 2 | 1 | 1 | 1 | 1 |
| 10 | 5.7 | 0.57 | | | | | | | | |

[illegible][illegible]

TABLE IV: ACTIVITY OF AMINO ACID DERIVATIVES*

| Example # | Resistant | Sensitive | SA 446 | SA 489 | SA 447 | SA X400 | SA X778 | SA 491 | SA S13E | SA 1199 |
|-----------|-----------|-----------|--------|--------|--------|---------|---------|--------|---------|---------|
| 11 | 45 | 1.7 | 1 | 2 | 1 | 1 | 0.5 | 2 | 1 | 1 |
| 12 | 2.8 | 0.19 | 2 | 2 | 0.5 | 1 | 0.25 | 0.5 | 2 | 1 |
| 13 | 2.4 | 0.095 | 1 | 0.5 | 1 | 0.5 | 1 | 1 | 0.5 | 1 |
| 14 | >128 | 6.1 | | | | | | | | |
| 15 | 27 | 1.2 | 1 | 1 | 1 | 1 | 0.5 | 1 | 1 | 2 |
| 16 | >128 | 7 | | | | | | | | |
| 17 | >32 | 0.5 | 0.5 | 0.06 | 0.5 | 0.06 | 0.06 | 0.125 | 0.25 | 0.25 |
| 18 | 27 | 0.87 | 0.5 | 0.125 | 0.5 | 0.25 | 0.25 | s.06 | 0.5 | 0.5 |
| 19 | 64 | 2.6 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 |
| 20 | >128 | 2 | 0.5 | s.06 | 0.25 | s.06 | 0.25 | s.06 | 0.125 | 0.125 |
| 21 | 11 | 1.5 | 0.5 | 0.25 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |

| Example # | SA 1199A | SH 105 | SH 415 | SE 270 | EF 180 | EF 180-1 | EF 2041 | EF 276 | EG 245 | HFRD | EC 14 |
|-----------|-----------|--------|--------|--------|--------|----------|---------|--------|--------|------|-------|
| 11 | 1 | 0.5 | 1 | 0.5 | 8 | 0.25 | 1 | 2 | 1 | >64 | >64 |
| 12 | 0.25 | 0.125 | 0.25 | 0.125 | 1 | s.06 | 0.25 | 1 | 0.25 | 32 | >64 |
| 13 | 0.25 | 1 | 0.5 | 0.25 | 0.25 | s.06 | s.06 | 0.5 | s.06 | 16 | >64 |
| 14 | | | | | | | | | | | |
| 15 | 0.125 | 1 | 1 | 0.25 | 8 | s.06 | 0.25 | 0.5 | 1 | >64 | >64 |
| 16 | | | | | | | | | | | |
| 17 | s.06 | 0.5 | 1 | 0.25 | 1 | s.06 | s.06 | 0.06 | 0.06 | 32 | >64 |
| 18 | no growth | 1 | 1 | 0.25 | 2 | 0.5 | s.06 | 0.5 | 1 | 16 | >64 |
| 19 | no growth | 4 | 4 | 2 | 8 | 1 | 0.5 | 2 | 2 | >64 | >64 |
| 20 | no growth | 8 | 16 | 0.125 | 16 | 0.25 | s.06 | 0.125 | 0.5 | 8 | >64 |
| 21 | no growth | 2 | 2 | 0.5 | 1 | 0.5 | 0.5 | 1 | 1 | 2 | >64 |

TABLE IV (continued)

| Example # | Resistant | Sensitive | SA 446 | SA 489 | SA 447 | SA X400 | SA X778 | SA 491 | SA S13E | SA 1199 |
|-----------|-----------|-----------|--------|--------|--------|---------|---------|--------|---------|---------|
| 22 | 6.7 | 0.66 | 1 | 1 | 1 | 0.5 | 1 | 0.5 | 2 | 2 |
| 23 | 2 | 0.29 | 1 | 0.5 | 1 | 2 | 2 | 0.5 | 2 | 0.5 |
| 24 | >128 | 4 | 4 | 2 | 4 | 2 | 1 | 1 | 2 | 2 |
| 25 | 27 | 1.3 | 4 | 1 | 2 | 2 | 2 | 2 | 2 | 1 |
| 26 | 23 | 0.76 | 2 | 0.5 | 1 | 0.5 | 0.5 | ≤0.06 | 1 | 1 |
| 27 | 16 | 1 | 2 | 4 | 1 | 2 | 1 | 1 | 2 | 1 |
| 28 | 13 | 1.7 | 4 | 1 | 2 | 2 | 1 | 2 | 2 | 2 |
| 29 | 27 | 1.2 | 2 | 0.25 | 0.5 | 0.25 | 0.125 | ≤0.06 | 0.5 | 0.125 |
| 30 | 38 | 2.3 | 8 | 1 | 2 | 2 | 1 | 2 | 2 | 2 |
| 31 | 5.6 | 0.33 | 0.5 | 2 | 2 | 2 | 0.5 | 0.5 | 1 | 0.5 |

| Example # | SA 1199A | SH 105 | SH 415 | SE 270 | EP 180 | EP 180-1 | EP 2041 | EP 276 | EG 245 | HFRD | EC 14 |
|-----------|----------|--------|--------|--------|--------|----------|---------|--------|--------|------|-------|
| 22 | 0.25 | 2 | 4 | 0.25 | 2 | ≤0.06 | 1 | 1 | 0.25 | >64 | >64 |
| 23 | 0.25 | 1 | 1 | 0.125 | 0.5 | ≤0.06 | 0.5 | 0.25 | 0.125 | >64 | >64 |
| 24 | 1 | 16 | 32 | 2 | >64 | 1 | 1 | 1 | 8 | >64 | >64 |
| 25 | 0.5 | 2 | 4 | 2 | 8 | ≤0.06 | 1 | 2 | 2 | >64 | >64 |
| 26 | 0.125 | 1 | 2 | 0.25 | 4 | ≤0.06 | 0.25 | 1 | 0.5 | >64 | >64 |
| 27 | 0.5 | 0.125 | 2 | 0.25 | 4 | 0.25 | 1 | 1 | 0.5 | 64 | >64 |
| 28 | 1 | 2 | 4 | 1 | 2 | 0.5 | 2 | 1 | 2 | >64 | >64 |
| 29 | ≤0.06 | 0.125 | 0.5 | ≤0.06 | 4 | ≤0.06 | 0.125 | 0.25 | 2 | >64 | >64 |
| 30 | 1 | 2 | 2 | 1 | 8 | 0.5 | 1 | 2 | 2 | >64 | >64 |
| 31 | 0.25 | 0.5 | 2 | 0.5 | 1 | 0.25 | 1 | 2 | 0.5 | >64 | >64 |

TABLE IV (continued)

| Example # | Resistant | Sensitive | SA 446 | SA 489 | SA 447 | SA X400 | SA X778 | SA 491 | SA S13E | SA 1199 |
|-----------|-----------|-----------|--------|--------|--------|---------|---------|--------|---------|---------|
| 32 | 16 | 0.76 | 1 | 1 | 1 | 2 | 0.5 | 0.125 | 0.25 | 0.25 |
| 33 | 27 | 2.6 | 1 | 2 | 1 | 1 | 1 | 0.5 | 1 | 0.5 |
| 34 | 38 | 0.44 | 0.125 | ≤.06 | 0.125 | ≤.06 | ≤.06 | ≤.06 | ≤.06 | 0.125 |
| 35 | 4.8 | 0.66 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 |
| 36 | >128 | 16 | 8 | 4 | 16 | 4 | 4 | 2 | 4 | 4 |
| 37 | >32 | 0.87 | 0.5 | 0.25 | 1 | 0.25 | 0.25 | 0.5 | 0.25 | 0.5 |
| 38 | 6.7 | 0.19 | 1 | 0.25 | 1 | 1 | 0.5 | ≤.06 | 0.5 | 1 |
| 39 | 45 | 0.38 | ≤.06 | ≤.06 | 0.5 | ≤.06 | ≤.06 | ≤.06 | 0.125 | 0.125 |
| 40 | >128 | 9.2 | 4 | 4 | 8 | 4 | 4 | 2 | 4 | 4 |
| 41 | >128 | 84 | 32 | 16 | 32 | 16 | 8 | 4 | 16 | 16 |
| 42 | 128 | 0.66 | 0.5 | 0.5 | 0.5 | 0.5 | 2 | 1 | 1 | 1 |

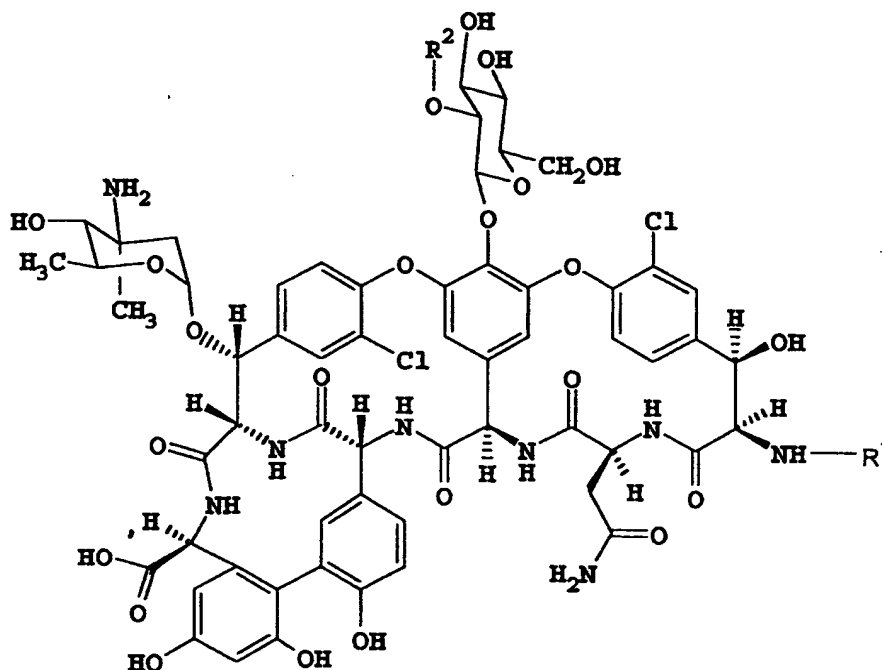
| Example # | SA 1199A | SH 105 | SH 415 | SE 270 | EP 180 | EP 180-1 | EP 2041 | EP 276 | EG 245 | HFRD | EC 14 |
|-----------|----------|--------|--------|--------|--------|-----------|---------|--------|--------|-----------|-------|
| 32 | ≤.06 | 0.125 | 0.5 | 0.125 | 2 | 0.125 | 1 | 2 | 0.5 | >64 | >64 |
| 33 | 0.25 | 0.5 | 0.5 | 0.25 | 4 | 0.5 | 2 | 4 | 1 | >64 | >64 |
| 34 | ≤.06 | ≤.06 | 4 | 0.25 | 2 | ≤.06 | 0.25 | ≤.06 | ≤.06 | 64 | >64 |
| 35 | 1 | 0.5 | 2 | 1 | 1 | 0.25 | 0.5 | 1 | 1 | >64 | >64 |
| 36 | 4 | 2 | >64 | 16 | >64 | 4 | 8 | 4 | 16 | >64 | >64 |
| 37 | 0.125 | 0.25 | 4 | 0.5 | >64 | 0.25 | 0.5 | 0.25 | 0.5 | 64 | >64 |
| 38 | ≤.06 | 1 | 1 | 1 | 2 | no growth | ≤.06 | 0.25 | 0.5 | no growth | >64 |
| 39 | ≤.06 | 0.5 | 2 | 0.25 | 2 | no growth | ≤.06 | ≤.06 | 0.5 | no growth | >64 |
| 40 | 2 | 4 | 64 | 4 | >64 | 4 | 2 | 1 | 16 | >64 | >64 |
| 41 | 8 | 16 | 64 | 8 | >64 | 4 | 8 | 8 | >64 | no growth | >64 |
| 42 | | 0.5 | 1 | 1 | 64 | | | | | | >64 |

| Abbreviations | Organism |
|---------------|---|
| Resistant | <i>Enterococcus faecium</i> and <i>faecalis</i> (geometric mean of 4-6 isolates) |
| Sensitive | <i>Enterococcus faecium</i> and <i>faecalis</i> (geometric mean of 4-6 isolates) |
| SA 446 | <i>Staphylococcus aureus</i> 446 |
| SA 489 | <i>Staphylococcus aureus</i> 489 |
| SA 447 | <i>Staphylococcus aureus</i> 447 |
| SA X400 | <i>Staphylococcus aureus</i> X400 |
| SA X778 | <i>Staphylococcus aureus</i> X778 |
| SA 491 | <i>Staphylococcus aureus</i> 491 |
| SA S13E | <i>Staphylococcus aureus</i> S13E |
| SA 1199 | <i>Staphylococcus aureus</i> SA1199 |
| SA 1199A | <i>Staphylococcus aureus</i> SA1199A |
| SH 105 | <i>Staphylococcus haemolyticus</i> 105 |
| SH 415 | <i>Staphylococcus haemolyticus</i> 415 |
| SE 270 | <i>Staphylococcus epidermidis</i> 270 |
| EF 180 | <i>Enterococcus faecium</i> 180 |
| EF 180-1 | <i>Enterococcus faecium</i> 180-1 |
| EF 2041 | <i>Enterococcus faecalis</i> 2041 |
| EF 276 | <i>Enterococcus faecalis</i> 276 |
| EG 245 | <i>Enterococcus gallinarum</i> 245 |
| HFRD | <i>Haemophilus influenzae</i> RD |
| EC 14 | <i>Escherichia coli</i> EC14 |

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WE CLAIM:

1. A compound of the formula



5

wherein R¹ represents

alkanoyl of C₂-C₁₀ which is unsubstituted, or which is substituted by a phenyl, or which is substituted on other than the α-carbon atom by an amino or protected amino group;

10 benzoyl or substituted benzoyl bearing one or two substituents each of which is independently halo, loweralkyl of C₁-C₄, loweralkoxy of C₁-C₄ or phenyl;

an acyl derived from an α-amino acid or an acyl derived from a protected α-amino acid, said α-amino acid being
15 selected from the group consisting of:

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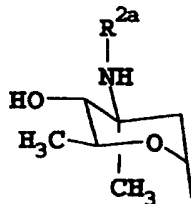
alanine,
arginine,
asparagine,
5 aspartic acid,
cysteine,
glutamic acid,
glutamine,
glycine,
10 histidine,
isoleucine,
leucine,
lysine,
methionine,
15 3-phenylalanine,
3- (p-chlorophenyl)alanine,
proline,
serine,
threonine,
20 tryptophan and
valine,

in either D- or L-form; or

an acyl derived from an α -amino acid as defined
above which bears on the amine a substituent which is alkyl
25 of C₁-C₁₀, benzyl, phenylbenzyl, or p-chlorobenzyl, with the
proviso that the acyl derived from N-methyl-D-leucine is
excluded;

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R^2 represents hydrogen or an epivancosaminyloxy of the formula



5

wherein R^{2a} represents hydrogen or $-CH_2-R^3$; and R^3 represents hydrogen,

alkyl of C_1-C_{11} ,

alkyl of $C_1-C_{11}-R^4$, or

10 $R^4 - (\text{linker})_{(0 \text{ or } 1)} - R^4)_{0 \text{ or } 1}$,

wherein each R^4 is independently phenyl or phenyl

substituted by one or two substituents, each of which is independently halo, loweralkyl of C_1-C_8 , loweralkoxy of C_1-C_8 , loweralkylthio of C_1-C_4 , or trifluoromethyl, and

15 "linker" is $-O-$, $-CH_2-$, or $-O-(CH_2)_n-$ wherein n is 1-3;

2. A compound of Claim 1 in which R^2 is an epivancosaminyloxy radical wherein R^{2a} represents hydrogen,

3. A compound of Claim 2 in which R^2 is an epivancosaminyloxy radical wherein R^{2a} represents $-CH_2-R^3$.

20 4. A compound of Claim 3 in which R^3 is p-biphenylyl.

5. A compound of Claim 3 in which R^3 is p-(p-chlorophenyl)phenyl.

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6. A pharmaceutical formulation comprising a compound of any of Claims 1-5 in combination with a pharmaceutically-acceptable diluent or carrier.

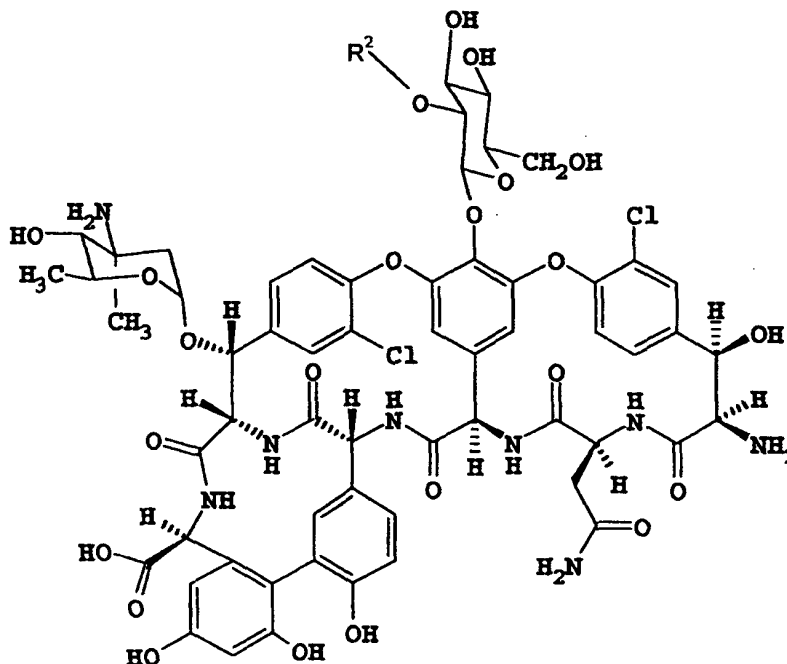
7. A method of treating a bacterial infection in a host comprising the step of administering to the host an effective amount of a formulation of Claim 6.

8. A method of Claim 7 wherein the bacterial infection is attributable to a vancomycin-resistant-enterococcus.

9. A compound of any of Claims 1-5 for use in antibacterial therapy.

10. A compound of any of Claims 1-5 for use in antibacterial therapy against vancomycin-resistant-enterococcus.

11. A process for the preparation of a compound as claimed in any one of Claims 1-5 which comprises reacting a parent glycopeptide of the formula



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/04306

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 38/00

US CL :514/2, 8, 9, 11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 8, 9, 11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, STN

search terms: A82486?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | US 5,591,714 A (NAGARAJAN et al) 07 January 1997, col.5, lines 20-30. | 1-11 |
| X | US 5,312,738 A (HAMILL et al) 17 May 1994, col.2, lines 40-55. | 1-11 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
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Date of the actual completion of the international search

25 MAY 1999

Date of mailing of the international search report

17 JUN 1999

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